1320453

PATENT SPECIFICATION

(11) 1 320 453

NO DRAWINGS

(21) Application No. 7708/71 (22) Filed 24 March 1971

(23) Complete Specification filed 11 Feb. 1972

(44) Complete Specification published 13 June 1973

(51) International Classification C07C 93/06; C07D 27/04, 51/70, 87/32, 87/54; A61K 27/00

(52) Index at acceptance
C2C 220 227 22Y 29X 29Y 30Y 323 32Y 360 362 364 36Y 3A13A1A4 3A13A1K 3A13C10C 3A13C10D 3A13C10F 3A13C10H 3A13C6B 3A13C9 456 45Y 502 50Y 650 652 662 682 790 79Y LF

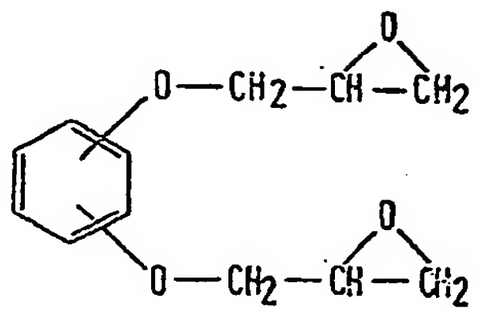
(72) Inventors K. BINOVIC, H. BRISSON and S. VRANCEA

(54) AROMATIC DIETHERS

(71) We, LABORATOIRES BIOSEDRA, a French Body corporate of 42, Avenue Augustin Dumont, Malakoff, (Hauts-de-Seine), France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with new chemical compounds and the preparation thereof, and compositions containing them.

It has now been found, in accordance with the present invention, that certain new aromatic diethers, as hereinafter defined, possess interesting pharmacological activity, for example sedative beta-blocking, anti-inflam- [illegible] anti-hypertensive activity



with the desired amine, suitably in a molar ratio of at least one mole of amine per mole of bis epoxyether. The bis(2,3-epoxy-propoxy) benzene may be prepared by reacting a dihydroxy benzene with an epihalohydrin, especially epichlorohydrin.

As stated above, the new compounds of the

PATENTS ACT 1949

SPECIFICATION NO 1320453

In accordance with the Decision of the Principal Examiner, acting for the Comptroller-General, dated 4 April 1974 this Specification has been amended under Section 14 in the following manner:-

Page 1, line 23, page 5, line 14, *delete* a hydrogen atom or

THE PATENT OFFICE
9 May 1974

R 74687/7

different and each is a hydrogen atom or [illegible] alkyl group or R^1, and R^2 together with the adjacent nitrogen atom form a heterocyclic ring which may contain another heteroatom, or the two groups NR^1R^2 together form a diamino group such as a piperazino or ethylene diamino group. Examples of the groups NR^1R^2, when they are not combined together, include diethylamino, methylpiperazino, hydroxypropylpiperazino, morpholino and pyrrolidino groups.

The new compounds may be prepared by reacting a -bis(2,3-epoxy-propoxy) benzene of the formula:—

[illegible] diether, in association with a conventional suppository base.

In order that the invention may be well understood, the following Examples are given by way of illustration only.

Example 1

A mixture of 33 grams (0.15 mole) of 1,4-bis(2,3 - epoxy - propoxy) - benzene and 40 grams (0.4 mole) of N-methylpiperazine in 180 ml alcohol are refluxed for 4 hours. The solvent is then distilled off on a water bath

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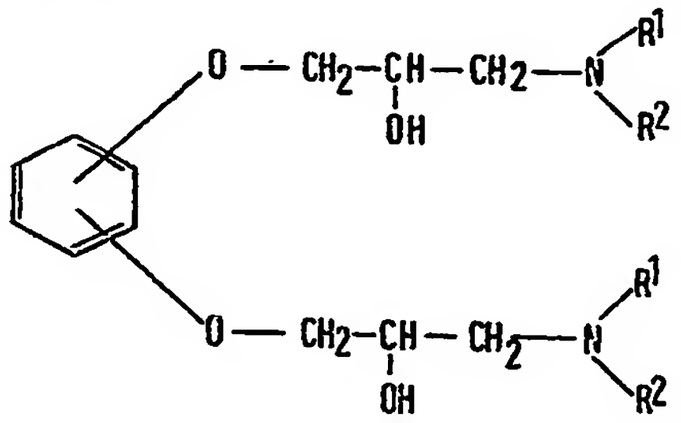
This invention is concerned with new chemical compounds and the preparation thereof, and compositions containing them.

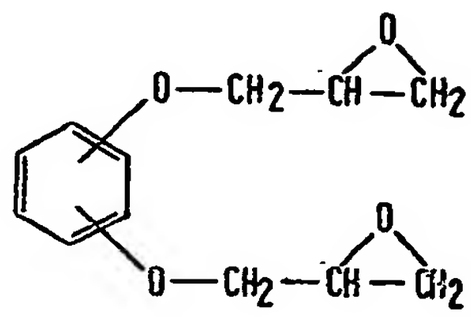
It has now been found, in accordance with the present invention, that certain new aromatic diethers, as hereinafter defined, possess interesting pharmacological activity, for example sedative beta-blocking, anti-inflammatory and anti-hypertensive activity.

According to the invention, therefore, there are provided as new compounds, aromatic diethers of the formula:



in which R^1 and R^2 are the same or are different and each is a hydrogen atom or an alkyl group or R^1, and R^2 together with the adjacent nitrogen atom form a heterocyclic ring which may contain another heteroatom, or the two groups NR^1R^2 together form a diamino group such as a piperazino or ethylene diamino group. Examples of the groups NR^1R^2, when they are not combined together, include diethylamino, methylpiperazino, hydroxypropylpiperazino, morpholino and pyrrolidino groups.

The new compounds may be prepared by reacting a -bis(2,3-epoxy-propoxy) benzene of the formula:—



with the desired amine, suitably in a molar ratio of at least one mole of amine per mole of bis epoxyether. The bis(2,3-epoxy-propoxy) benzene may be prepared by reacting a dihydroxy benzene with an epihalohydrin, especially epichlorohydrin.

As stated above, the new compounds of the invention have interesting pharmacological properties and, accordingly, another embodiment of the invention is for a pharmaceutical composition containing an aromatic bis ether in accordance with the invention together with a pharmaceutcal carrier or diluent.

The pharmaceutical compositions of the invention may, for example, be intended for administration by injection and may take the form of a solution or suspension in sterile pyrogen-free water or an injectible oil. Alternatively, the compositions of the invention may be formulated for oral administration, for example as tablets, pills, dragees, syrups or elixirs. Finally, the compositions of the invention may be formulated as suppositories and comprise the active ingredient, the aromatic diether, in association with a conventional suppository base.

In order that the invention may be well understood, the following Examples are given by way of illustration only.

Example 1

A mixture of 33 grams (0.15 mole) of 1,4-bis(2,3 - epoxy - propoxy) - benzene and 40 grams (0.4 mole) of N-methylpiperazine in 180 ml alcohol are refluxed for 4 hours. The solvent is then distilled off on a water bath

to give a white precipitate which is recrystallised from ethyl acetate to give 30 grams (47%) of the diamine having the characteristics shown in Table 1 below.

Example 2

A mixture of 55 grams (0.25 moles) of 1,4 - bis(2,3 - epoxy - propoxy) - benzene and 35.5 grams (0.5 mole) of pyrrolidine in 30 ml of ethyl alcohol is refluxed for 4 hours. The solvent is then evaporated off on a water bath to give a pasty product which crystallises out on standing.

The crystalline product is dissolved in the minimum of alcohol and then refluxed for a quarter of an hour in the presence of active carbon. The active carbon is filtered off and the solvent evaporated off to give 59 grams (65%) of crystalline diamine having the characteristics given in Table 1 below.

Example 3

A mixture of 33 grams (0.15 mole) of 1,4-bis(2,3 - epoxy - propoxy) - benzene and 12.91 grams (0.15 mole) of anhydrous piperazine in 180 ml of absolute ethyl alcohol are refluxed for 4 hours.

The reaction mixture is cooled and the white precipitate obtained is filtered off, washed with ether and recrystallised from ethyl acetate to give 35 grams (76%) of the amine having the characteristics given in Table 1.

Table 1 shows the characteristics of the products obtained in the three above Examples together with those of other products prepared in accordance with the invention by a similar method.

TABLE 1

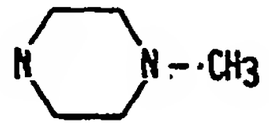
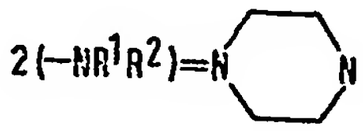
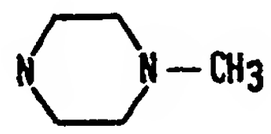
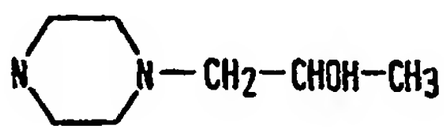
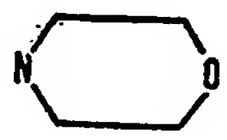
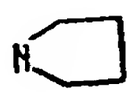
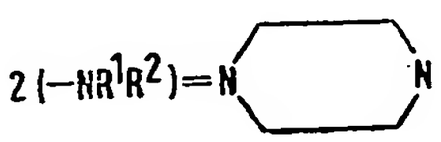
Compound No.	Position of Substituents on benzene ring	—NR^1R^2	Melting Point (°C)
I (Example I)	I, 4		110—112
2 (Example 2)	I, 4		94
3 (Example 3)	I, 4		216
4	I, 3	$N(C_2H_5)_2$	gum (dihydrochloride
5	I, 4	"	60
6	I, 3		72
7	I, 3		113 — 115
8	I, 4	"	147 — 148
9	I, 3		94
10	I, 4	"	147 — 148

TABLE 1 (Continued)

Compound No.	Position of Substitutents on benzene ring	—NR^1R^2	Melting Point) (°C)
11	I, 3		127 (dihydrochloride
12	I, 3		92
13	I, 4	$2(-NR^1R^2) = NH - CH_2 - CH_2 - NH$	131 — 133

It will be understood that in the case of compounds Nos. 3, 12 and 13, the two NR^1R^2 substituents are combined to form a diamino radical.

All the compounds listed above possess interesting pharmacological activity and also have a low toxicity indicated in Table 2 below.

TABLE 2

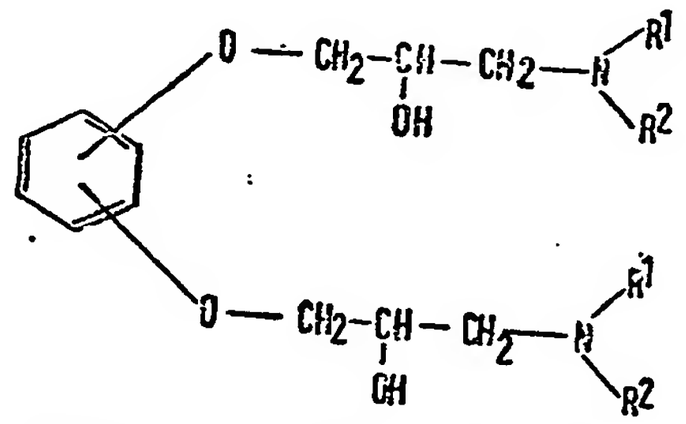
Compound No.	LD_{50} (mg/kg)		
	i.v.	i.p.	Oral
1	29	195	400
2	15.8	43	172
3	67	270	1200
4	81.5	330	980
5	63	114	580
6	7	22.5	400
7	69	305	1000
8	72.5	348	600
9	312	1000	1200
10	290	800	—
11	23.5	50	345
12	15	40	1000
13	3.65	8.50	520

The compounds according to the invention are active by the mouth when administered two or three times per day in doses from 50 to 300 milligrams.

Compound No. 2 is markedly active, at these doses, and manifests sedative, dimetic and hypertensive effects while Compound No. 3 is active as an anti-inflammatory agent.

WHAT WE CLAIM IS:—

1. As new chemical compounds, aromatic diethers of the formula:—



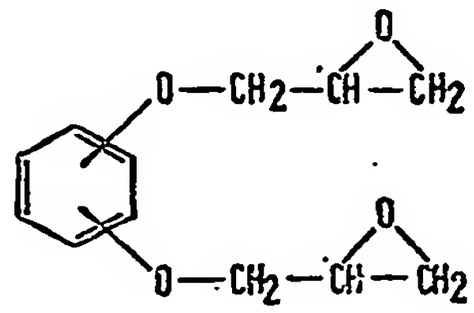
in which R^1 and R^2 are the same or are different and each is a hydrogen atom or an alkyl group or R^1 and R^2 together with the adjacent hydrogen atom form a heterocyclic ring which may contain another hetero atom, or the two groups $—NR^1R^2$ together form a diamino group.

2. Compounds as claimed in claim 1 in which the group $—NR^1R^2$ is a diethylamino, methylpiperazino, hydroxypropylpiperazino, morpholino or pyrrolidino group.

3. Compounds as claimed in claim 1 in which the two groups $—NR^1R^2$ together form a piperazino or ethylene diamino group.

4. Compounds as claimed in claim 1 as disclosed herein.

5. A process for the preparation of compounds as claimed in claim 1 which comprises reacting a bisepoxy compound of the formula:



with an amine of the formula HNR^1R^2, in which R^1 and R^2 have the meanings defined in claim 1.

6. A process as claimed in claim 5 in which the amine and bisepoxy compound are reacted in a molar ratio of at least 1:1.

7. A process as claimed in claim 5 substantially as hereinbefore described with reference to the Examples.

8. A pharmaceutical composition comprising a compound as claimed in any one of claims 1—4 in association with a pharmaceutical carrier or diluent.

9. A pharmaceutical composition as claimed in claim 8 substantially as hereinbefore described.

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